Final Analysis of the Phase 1a/b Study of Fibril-Reactive Monoclonal Antibody 11-1F4 (CAEL-101) in Patients with AL Amyloidosis

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CAEL101 Directly Targets AL Amyloid

- Amyloid-fibril reactive monoclonal antibody IgG1κ 11-1F4
  - recognizes a conformational neoepitope
  - dissolution of human λ and κ amyloidomas in mice

- Chimerized GMP-grade amyloid fibril-reactive IgG1 11-1F4 mAb (CAEL-101) was produced by NCI’s Biological Resource Branch

- Open-label, dose-escalation phase 1a/b study for patients with relapsed or refractory AL Amyloidosis
Study Objectives

Primary Objective:
• Establish the maximum tolerated dose (up to 500 mg/m²)

Secondary Objectives:
• Demonstrate reduction in amyloid burden

• Determine the pharmacokinetics and safety at different dose levels

• Determine whether there is a dose response at the highest doses

https://clinicaltrials.gov/ct2/show/NCT02245867
### Eligibility

#### KEY INCLUSION CRITERIA

- Confirmed diagnosis of AL amyloidosis
- Received prior systemic therapy
- Does not require plasma cell targeted therapy
- Age > 21 years
- ECOG performance status ≤ 3

#### KEY EXCLUSION CRITERIA

- EF < 40%
- Intraventricular Septum > 25mm
- Creatinine clearance < 30 cc/min
- Alkaline phosphatase > 3 times institutional upper limit of normal
- Bilirubin > 3.0 mg/dL
Dose Escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>0.125</td>
</tr>
<tr>
<td>-1</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>0.5*</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>250</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
</tr>
</tbody>
</table>

**Phase 1a**
- 8 patients

**Phase 1b**
- 19 patients

Ch 11-1F4 mAb (CAEL-101) infusion
Clinical Evaluation

https://clinicaltrials.gov/ct2/show/NCT02245867

March 27, 2018
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (N=27 patients)</strong></td>
<td>66 yrs (Range: 34 – 79)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>N=19 (70%)</td>
</tr>
<tr>
<td>Female</td>
<td>N=8 (30%)</td>
</tr>
<tr>
<td><strong>Light Chain type</strong></td>
<td></td>
</tr>
<tr>
<td>(\lambda)</td>
<td>N=15 (56%)</td>
</tr>
<tr>
<td>(\kappa)</td>
<td>N=12 (44%)</td>
</tr>
<tr>
<td><strong>Revised Mayo Stage</strong></td>
<td>II (Range: I to IV)</td>
</tr>
<tr>
<td><strong>Organ Involvement (No.)</strong></td>
<td>2 (Range: 1 – 4)</td>
</tr>
<tr>
<td>Heart</td>
<td>N=16 (59%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>N=13 (48%)</td>
</tr>
<tr>
<td>Skin/Soft tissue</td>
<td>N=12 (44%)</td>
</tr>
<tr>
<td>GI</td>
<td>N=8 (30%)</td>
</tr>
<tr>
<td>Nervous system (11%)</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Liver</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Lung</td>
<td>N=1 (4%)</td>
</tr>
<tr>
<td><strong>Best Hematologic Response to Plasma Cell Directed Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>N=4 (15%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>N=19 (70%)</td>
</tr>
<tr>
<td>PR</td>
<td>N=2 (7%)</td>
</tr>
<tr>
<td>NR</td>
<td>N=2 (7%)</td>
</tr>
<tr>
<td><strong>Previous Plasma cell Directed Therapy (No.)</strong></td>
<td>2 (Range: 1 – 9)</td>
</tr>
<tr>
<td>1 Regimen 30% (N=8), 2 Regimen 30% (N=8), ≥3 Regimen 40% (N=11)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline NT-proBNP (ng/L)</strong></td>
<td>1915 (Range: 815.5 – 8274)</td>
</tr>
<tr>
<td><strong>Baseline 24 hr Urine Protein (mg/24hr)</strong></td>
<td>4796 (Range: 1078 – 10,260)</td>
</tr>
<tr>
<td><strong>Time Since last Exposure to Chemotherapy (mos)</strong></td>
<td>6 (Range 1 – 51)</td>
</tr>
</tbody>
</table>

*Baseline NT-proBNP in patients with cardiac involvement who were evaluable for response (Baseline NT-proBNP ≥ 650pg/mL)*

*Baseline 24 hour urine protein in patients evaluable for renal response*
Phase 1a/b Results

• 27 patients accrued and evaluable for toxicity
  • No dose limiting toxicity to a Maximum tolerated dose of 500mg/m²
  • No drug-related deaths

• 24 Patients evaluable for response
  • N = 3 had no measurable disease

• 67% (12 out of 18 patients) with cardiac and/or renal involvement showed a response

• 3 Patients with involvement of other organs had response
  • 1 GI response (n = 4)
  • 1 Liver response (n = 2)
  • 1 soft tissue response with improvement of arthritis Grade 3 to 1 (n = 4)

• Overall Median Time to response was 3 weeks after the first dose of CAEL-101
Best Cardiac Response After Treatment with CAEL-101

Cardiac Response Criteria

Baseline NT-proBNP ≥650 pg/ml and at least one post-baseline NT-proBNP measurement

12 patients evaluable for response

8 responders – 67%
4 stable

Median time to cardiac response -3 weeks

Percent change in baseline NT-proBNP (%)

PROGRESSION
>30% and >300 pg/ml increase in NT-proBNP

STABLE

RESPONSE
>30% and >300 pg/ml decrease in NT-proBNP

March 27, 2018
Sustained Decrease in NT-proBNP After Treatment with CAEL-101 in Phase 1b

Following 4 weekly doses of CAEL-101, there was a sustained decrease in NT-proBNP from baseline.
Patient 1-21B, 250mg/m², Dose Level 6

Baseline GLS -9.58
NTproBNP 2549pg/mL

Improved GLS -13.39
NTproBNP 1485 pg/mL
GLS versus Change in NT-proBNP For Cardiac Evaluable Patients Treated with CAEL-101

Evaluable patients
n = 8

- An improvement in GLS corresponds to a more negative number.
- As NT-proBNP improved, so did GLS.
- The Pearson Correlation is 0.345
Best Renal Response After Treatment with CAEL-101

- 10 patients evaluable for response
- 5 responders – 50%
- 5 stable

Median time to renal response – 4 weeks*

*24 hour urine protein measured at screening and Week 8 in Phase 1a and at screening and Weeks 5, 8 and 12 in Phase 1b
Organ Response Occurs Independent of Depth of Response to Chemotherapy

- Patient with cardiac Lambda AL Amyloidosis
- 6 prior treatments with best Hematologic Response PR
- Prior to CAEL-101 NO Organ response
Summary and Future Outlook

- Treatment with CAEL-101 is well tolerated and safe

- CAEL-101 is clinically efficacious
  - early organ response
  - Cardiac, Renal, GI, Liver and Soft tissue

- CAEL-101 represents a promising treatment for AL Amyloidosis
  - reduces amyloid burden and leads to improvement in organ function
  - possible simultaneous induction of hematologic and organ response to:
    - preserve organ function
    - allow for auto-SCT
    - improve survival

- Multicenter Phase 2 SWOG trial
- Phase 3 trial conducted by Caelum Biosciences
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